Ablation of Atrial Fibrillation

Learning by Ablating

Nassir F. Marrouche, MD @nmarrouche

Executive Director, Comprehensive Arrhythmia Research and Management Center (CARMA)

Director, Electrophysiology Laboratories

University of Utah
Disclosures

Consulting, honoraria, stock options

- Biosense Webster, Sanofi-Aventis, MRI Interv, BMS, Boehringer-Ingelheim, Biotronik, Ecardio, St Jude, Medtronic, Arapeen Med, MARREK Inc, Daiishi Sayko, Cardiac Designs, Arapeen Med, VytronUs

Research grants

- NIH, MRI Interv, Sanofi, Biosense, BI, Biotronik, MARREK Inc., Medtronic, Boston Scientific, Catheter Robotics, VytronUs
Outline

• Pulmonary Vein Isolation

• Everything Else

• Substrate

• …and the WHY?
PV-Triggers initiating AF

LA

LAA

PV

*
Left Upper PV trigger initiating AF
Ostial/Antral initiation of AF after Distal Isolation

STARAF-II

PVI

Complex Fractionated Electrograms

Linear Ablation

Among patients with persistent atrial fibrillation, no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation.
TARGETING ROTATIONAL ACTIVITIES
Atrial Fibrillation Ablation Results

- Ouyang et al. 2010, Circulation
- Weersooriya et al. 2011, JACC
- Verma et al., NEJM 2015; 372: 1812-1822
- Wokhlu et al. 2010, JCE
- Winkle RA, Am Heart J 2011
- Kuck et al., NEJM 2016; 23:2235-2245
The Substrate
Correlation of atrial LGE-MRI with human tissue sample

3D DE-MRI image

Masson trichome staining
- Myocyte in red
- Collagen in blue

Myocyte subtraction image

McGann et al. Circ Arrhythm Electrophysiol. 2013 Dec 20
Patchy fibrotic atrial disease in patients with AF
Progression of fibrosis in AF independent of AF burden

Figure 2: LGE MRI of the left atrium of two patients: Panel A&B is LA MRI of patient with stable fibrosis, Panel C&D is LA MRI of patient with progressive fibrosis.
Progression of fibrosis after AF ablation

Group 1

Group 2

Group 3

First scan

Second scan
Progression of fibrosis after AF ablation: *Increased risk of procedural failure*
AF Phenotype and Stage of Atrial Disease

- **Utah I <10 fibrosis**
  - Persistent 48%
  - Paroxysmal 50%
  - Permanent 2%

- **Utah II >10-20%**
  - Persistent 52%
  - Paroxysmal 46%
  - Permanent 2%

- **Utah III >20-30%**
  - Persistent 55%
  - Paroxysmal 42%
  - Permanent 3%

- **Utah IV >30%**
  - Persistent 74%
  - Paroxysmal 17%
  - Permanent 9%
Original Investigation

Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation
The DECAAF Study

Naveen F. Maisel, MD, David Wiler, MD, Gerhard Heidbrink, MD, Reiner Jost, MD, Naveen Maisel, MD, Franci Marbet, MD, Eugene Robinson, PhD, Nathaniel Bucy, BS, Nan Hu, PhD, Lisa Hart, MD, Thomas Dornics, MD, Martin Doehring, MD, Thomas Greiner, MD, Markus Mancuso, MD, Christian Wirtzfeld, MD, Berg Heiner, MD, Eric B. Strauss, MD, Eli M. Wasser, MD, Paul Lebrun, MD, Johannes Kuck, MD

IMPETUS. Left atrial fibrosis is prominent in patients with atrial fibrillation (AF). Extensive atrial tissue fibrosis is identified by delayed enhancement magnetic resonance imaging (DEMRI) has been associated with poor outcomes of AF catheter ablation.

OBJECTIVE. To characterize the feasibility of atrial tissue fibrosis estimation by delayed enhancement MRI and its association with subsequent AF ablation outcome.

DESIGN, SETTING, AND PARTICIPANTS. Multicenter, prospective, observational cohort study of patients diagnosed with paroxysmal and persistent AF undergoing their first catheter ablation (conducted between August 2009 and August 2011 at 15 centers in the United States, Europe, and Australia). Delayed enhancement MRI images were obtained up to 30 days before ablation.

MAIN OUTCOMES AND MEASURES. Fibrosis quantification was performed at a core laboratory blinded to the participating center, ablation approach, and procedure outcome. Fibrosis blinded to the treating physician was categorized as stage 1 (10% of the atrial wall), stage 2 (10% to 30%), stage 3 (30% to 70%), and stage 4 (>70%). Patients were followed up for recurrent atrial fibrillation per current guidelines using electrocardiography or ambulatory monitor recording, and results were analyzed at a core laboratory. Cumulative incidence of recurrence was estimated by stage at days 30 and 45 after a 10-day blanking period (fixed time allowed for antiarrhythmics related to ablation-induced inflammation to subside) and the risk of recurrence was estimated (adjusting for 10 demographic and clinical covariates).

RESULTS. Atrial tissue fibrosis estimation by delayed enhancement MRI was successfully quantified in 272 of 329 enrolled patents (83% of the patients were included due to poor MRI quality). There were 330 patients who were followed up after the blanking period (mean [SD] age of 53 [12] years, 51% male, and 61% with paroxysmal AF). For recurrent atrial fibrillation, the unadjusted overall hazard ratio was 1.63 increase in left atrial fibrosis to 1.29 (95% CI, 1.01-1.08).

Estimated unadjusted cumulative incidence of recurrent atrial fibrillation for day 0 was 15.3% (95% CI, 7.6%-26.9%); stage 1, 3.2% (95% CI, 2.4%-4.9%); stage 2, 4.5% (95% CI, 3.8%-5.8%); stage 3, 4.0% (95% CI, 3.1%-5.8%); and stage 4, 5.0% (95% CI, 3.8%-7.2%). By day 450 was 15.3% (95% CI, 7.6%-26.9%); 36.6% (95% CI, 26.2%-47.6%); 45.5% (95% CI, 36.3%-56.6%); and 66.4% (95% CI, 46.6%-87.3%), respectively. Similar results were obtained after covariate adjustment. The addition of fibrosis to a recurrence prediction model that includes traditional clinical covariates resulted in an improved predictive accuracy with the C-statistic increasing from 0.65 to 0.69 (p = difference of 0.05, 95% CI, 0.25-0.05).

CONCLUSIONS AND RELEVANCE. Among patients with AF undergoing catheter ablation, atrial tissue fibrosis estimated by delayed enhancement MRI was independently associated with likelihood of recurrent atrial fibrillation. The clinical implications of this association warrant further investigation.


Author Affiliations. The full list of authors of the study article. Corresponding Author. Naveen F. Maisel, MD, University of Utah Health-Cr Se, 315 N 2000 E, Ivory A03, Salt Lake City, UT 84132 (nmasel@nh.uhc.utah.edu).

Copyright 2014 American Medical Association. All rights reserved.

jama.com
Classification of AF based on degree of atrial fibrosis

Stage 1: <10%
Stage 2: 10-20%
Stage 3: 20-30%
Stage 4: >30%

Healthy tissue
Fibrotic

JAMA. 2014 Feb 5;311(5):498-506
Degree of atrial fibrosis predicts AF treatment success

JAMA. 2014 Feb 5;311(5):498-506
Left Atrial LGE predicts Arrhythmia Recurrence Following Pulmonary Vein Isolation for AF

Fibrosis as a treatment target
DECAAF: 3 month follow up MRI
DECAAF: 3 month follow up MRI

Pulmonary Vein encirclement at follow-up

Number of Pulmonary Veins
Completely Encircled
in Patients undergoing PVI

Akoum et al. JCE. 2013 Oct;24(10):1104-9
DECAAF: Residual fibrosis after ablation at follow-up

Overlap of Scar + Fibrosis - Post-ablation Scar = Residual Fibrosis

Main Predictor | HR [95% CI]* | P-value
--- | --- | ---
% residual fibrosis | 1.081 [1.049 - 1.115] | <.0001

*per 1% change, adjusting for age, gender, hypertension, mitral valve disease

Akoum et al. JCE. 2015 May;26(5):473-80
Better Outcome when Ablating Fibrotic Tissue (DECAAF)

Akoum et al. JCE. 2013 Oct;24(10):1104-9
LA rotor cores were most commonly associated with isolated patchy fibrosis or at the border zones of more dense fibrosis as detected by DE-MRI.
Non Invasive imaging and noninvasive mapping: ECGI Rotor mapping

Jais et al.
Isolating and Ablating Fibrotic Tissue

Homogenizing Fibrotic Tissue
Management of AF guided by fibrosis imaging

- Fibrosis <10%
  - Healthy tissue
  - Fibrotic tissue
- Fibrosis ≥10%-<20%
  - Localized fibrosis
- Fibrosis ≥20%-<30%
  - Scattered fibrosis
- Fibrosis ≥30%
  - Non-ablative management or homogenization of fibrosis (awaiting DECAAF II)

PVI ± Homogenization of scar

Post-ablation recurrence

- No fibrosis progression
  - Extensive post-ablation scarring
  - ? Connection and homogenization of existing scar
- Extensive post-ablation progression of fibrosis
  - Post PVI scarring
  - Depth of ablation scar
  - 2.5mm
  - 1.25mm
  - 0mm
  - ? Re-isolation of PVs + connection of ablation scar + flutter line

Siebermeier et al JACCEP 2017
Efficacy of DE-MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation
DECAAF II

• Prospective (980 patients)
• Multicenter (42 sites)
• Randomized
• End point driven
Enrollment & Work Flow

- Patients with persistent AF
- ✓ Approach, Eligible?
- ✓ Consent
- Pre-ablation
  - DE-MRI
  - Randomization
  - ✓ Passes quality check

- Group 1
  - PVI ablation
  - MRI-fibrosis images not made available

- Group 2
  - Fibrosis-guided ablation
  - Images made available to site clinician

Daily ECG by smartphone after blanking period
Group 1--PVI
Group 2--Targeting fibrosis
Group 2--Targeting fibrosis
Why we ablate Atrial Fibrillation?
Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation

The CASTLE-AF trial

Late Breaking Trials ESC 2017
• Atrial fibrillation (AF) and heart failure are well intertwined

• Catheter ablation of AF in patients with heart failure has been shown feasible
CASTLE-AF

Rationale and Objective

• Study the effectiveness of catheter ablation of atrial fibrillation in patients with heart failure in improving hard primary endpoints of mortality and heart failure progression when compared to conventional standard treatment.
CASTLE-AF

**Primary Endpoint**

- **All-cause mortality**
- **Worsening heart failure admissions**

**Secondary Endpoints**

- All-cause mortality
- Worsening of heart failure admissions
- Cerebrovascular accidents
- Cardiovascular mortality
- Unplanned hospitalization due to cardiovascular reason
- All-cause hospitalization
- Quality of Life: Minnesota Living with Heart Failure and EuroQoL EQ-5D
- Exercise tolerance (6 minutes walk test)
- Number of delivered ICD shocks, and ATPs (appropriate/inappropriate)
- LVEF
- Time to first ICD shock, and time to first ATP
- Number of device detected VT/VF
- AF burden: cumulative duration of AF episodes
- AF free interval: time to first AF recurrence after 3 months blanking period post ablation

Marrouche et al. ESC 2017
CASTLE-AF

Inclusion Criteria

• Symptomatic paroxysmal or persistent AF
• Failure or intolerance to ≥ 1 or unwillingness to take AAD
• LVEF ≤ 35%
• NYHA class ≥ II
• ICD/CRT-D with Home Monitoring capabilities already implanted due to primary or secondary prevention

Marrouche et al. ESC 2017
Study Design—CASTLE-AF

- Investigator initiated, Prospective, Multicenter (31 sites, 9 countries), Randomized, Controlled

Eligibility Assessment

3013 pts

Enrolled/Randomized

397 pts

Run-in 5 weeks

200 pts

Ablation

179 pts

21 pts excluded

13 pts excluded

153 pts (26 cross-overs)

Follow-up: 3, 6, 12, 24, 36, 48, 60 months

ICD/CRT-D check
Adverse event documentation
Echocardiography
6-minute walk test
Optimization of medication for HF
Home Monitoring programming
NYHA, weight, BP, QoL
Patients’ diary

Conventional

184 pts

165 pts (18 cross-overs)

Marrouche et al. ESC 2017
According to the ACC/AHA/ESC 2006 guidelines for treatment of AF in Heart Failure patients

Efforts to maintain sinus rhythm in this study arm were recommended

In case of rate control strategy:
- 60 and 80 beats per minute at rest
- 90 and 115 beats per minute during moderate exercise

Anticoagulation was initiated, if not already started, and maintained throughout the study. The INR was maintained between 2.0 and 3.0
CASTLE AF
Ablation Protocol

- Pulmonary Vein Isolation
- Additional lesions
  - at discretion of operator
- Repeat ablation after blanking period

Marrouche et al. ESC 2017
<table>
<thead>
<tr>
<th></th>
<th>Ablation group (179 patients)</th>
<th>Conventional group (184 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>64 (56-71)</td>
<td>64 (56-73.5)</td>
</tr>
<tr>
<td>New York Heart Association class (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>II (%)</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>III (%)</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>IV (%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction – %</td>
<td>32.5 (25.0-38.0)</td>
<td>31.5 (27.0-37.0)</td>
</tr>
<tr>
<td>Current type of atrial fibrillation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal (%)</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Persistent (%)</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>CRT-D implanted (%)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>ICD implanted (%)</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

Baseline Characteristics-CASTLE AF

Marrouche et al. ESC 2017
## Baseline Characteristics-CASTLE AF

<table>
<thead>
<tr>
<th></th>
<th>Ablation group (179 patients)</th>
<th>Conventional group (184 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitor or ARB – no. (%)</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>Beta-blocker – no. (%)</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>Diuretic – no. (%)</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Digitalis – no. (%)</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Oral anticoagulant – no. (%)</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>Antiarrhythmic drug – no. (%)</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Amiodarone – no. (%)</td>
<td>97</td>
<td>85</td>
</tr>
</tbody>
</table>

Marrouche et al. ESC 2017
Results-CASTLE AF

Absolute change in LVEF from baseline

Marrouche et al. ESC 2017
### Results - CASTLE AF

#### Serious Adverse Events and Strokes

<table>
<thead>
<tr>
<th>Event</th>
<th>Ablation Group (n=179)</th>
<th>Conventional Group (n=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. patients with event (%)</td>
<td>no. patients with event (%)</td>
</tr>
<tr>
<td>Pericardial effusion (acute)</td>
<td>3 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Severe bleeding (acute)</td>
<td>3 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>7 (3.9)</td>
<td>12 (6.7)</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (1.7)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Groin infection</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Marrouche et al. ESC 2017
Results-CASTLE AF

Primary Composite Endpoint

Survival Probability

Follow-Up Time (Months)

Risk Reduction: 38%

Ablation

HR, \textbf{0.62} (95\% CI, 0.43-0.87); P=0.007

Log-rank test: P=0.006

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ablation</th>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td>179</td>
<td>184</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>141</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>
Results-CASTLE AF

All-Cause Mortality

Survival Probability

Follow-Up Time (Months)

0 12 24 36 48 60

Risk Reduction: 47%

Patients at Risk

Ablation 179 154 130 94 71 27
Pharmacological 184 168 138 97 63 19

HR, 0.53 (95% CI, 0.32-0.86); P=0.011
Log-rank test: P=0.009
Results - CASTLE AF

Worsening Heart Failure Admissions

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Ablation</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td>179</td>
<td>141</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>184</td>
<td>145</td>
</tr>
</tbody>
</table>

**Risk Reduction:** 44%

**HR, 0.56 (95% CI, 0.37-0.83); P=0.004**

Log-rank test: P=0.004
Results-CASTLE AF

Cardiovascular Mortality

Risk Reduction: 51%

Follow-Up Time (Months)

Patients at Risk

Ablation | 179 | 154 | 130 | 94 | 71 | 27
Pharmacological | 184 | 168 | 138 | 97 | 63 | 19

HR, 0.49 (95% CI, 0.29-0.84); P=0.009
Log-rank test: P=0.008
Results - CASTLE AF
Cardiovascular Hospitalization

Survival Probability

Follow-Up Time (Months)

Risk Reduction: 28%

Patients at Risk

<table>
<thead>
<tr>
<th>Method</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td>179</td>
<td>127</td>
<td>95</td>
<td>60</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>184</td>
<td>131</td>
<td>91</td>
<td>52</td>
<td>33</td>
<td>8</td>
</tr>
</tbody>
</table>

HR, 0.72 (95% CI, 0.52-0.99); P=0.041
Log-rank test: P=0.050
Results-CASTLE AF

**PVI vs PVI+**

No difference in primary endpoint, $p=0.7$

- PVI Only: 49
- PVI + Additional Ablations: 51
<table>
<thead>
<tr>
<th>Steering Committee</th>
<th>Data and Safety Monitoring Board</th>
<th>Co-Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johannes Brachmann</td>
<td>Etienne Aliot</td>
<td></td>
</tr>
<tr>
<td>Dietrich Andresen</td>
<td>Walter Lehmacher</td>
<td></td>
</tr>
<tr>
<td>Dietmar Bänsch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucas Boresma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luc Jordaens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heribert Schunkert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jürgen Siebels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juergen Vogt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Endpoint Adverse Event Committee</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heinrich Wieneke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frieder Braunschweig,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harriette F. Verwey</td>
<td></td>
</tr>
</tbody>
</table>

The study was funded by BIOTRONIK
LA rotor cores were most commonly associated with isolated patchy fibrosis or at the border zones of more dense fibrosis as detected by DE-MRI.
Non Invasive imaging and noninvasive mapping: ECGI Rotor mapping

*Jais et al.*
Isolating and Ablating Fibrotic Tissue

Homogenizing Fibrotic Tissue
Management of AF guided by fibrosis imaging

**Fibrosis <10%**
- Healthy tissue
- Fibrotic tissue

**Fibrosis ≥10%–<20%**
- Localized fibrosis

**Fibrosis ≥20%–<30%**
- Scattered fibrosis

**Fibrosis ≥30%**
- Non-ablative management or homogenization of fibrosis (awaiting DECAAF II)

**Post-ablation recurrence**

- **No fibrosis progression**
  - Extensive post-ablation scarring
  - Post PVI scarring
  - Depth of ablation scar

- **Extensive post-ablation progression of fibrosis**
  - 0mm
  - 1.25mm
  - 2.5mm
  - Ablation scar

? Connection and homogenization of existing scar
? Re-isolation of PVs
+ connection of ablation scar
+ flutter line

Siebermeier et al JACCEP 2017
Efficacy of DE-MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation
DECAAF II

• Prospective (980 patients)
• Multicenter (42 sites)
• Randomized
• End point driven
Enrollment & Work Flow

- Patients with persistent AF
  - ✔ Approach, Eligible?
  - ✔ Consent
  - ✔ Passes quality check

- Pre-ablation
  - DE-MRI
  - Randomization

- Group 1
  - PVI ablation

- Group 2
  - Fibrosis-guided ablation

Images made available to site clinician

MRI-fibrosis images not made available

Daily ECG by smartphone after blanking period
Group 1--PVI
Group 2--Targeting fibrosis
Group 2--Targeting fibrosis
....Why we ablate Atrial Fibrillation?
Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation

The CASTLE-AF trial

Late Breaking Trials ESC 2017
Atrial fibrillation (AF) and heart failure are well intertwined

Catheter ablation of AF in patients with heart failure has been shown feasible